REMARKS

Amendment of the Title

This amendment replaces the prior Title with a new Title that more closely mirrors the subject matter of the pending claims: a therapeutic combination of eplerenone, ramipril and a loop diuretic for treating heart failure post-acute myocardial infarction.

Amendments to the Claims

Claims 45-60 are pending. The present amendment cancels Claims 45-51 and amends Claim 52. Applicants reserve the right to file continuation applications with claims directed to the subject matter of cancelled Claims 45-51.

* * *

I. Amended Claim 52

The sole pending independent claim (Claim 52) now specifies a method for treating a subject having heart failure post-acute myocardial infarction by administering:

(a) about 1 mg to about 400 mg of eplerenone (an epoxy-steroidal aldosterone receptor antagonist);

(b) about 1 mg to about 200 mg of ramipril (an angiotensin converting enzyme inhibitor); and

(c) about 1 mg to about 200 mg of a loop diuretic.

Support for the claim amendment can be found in the specification as filed at, for example, page 38, lines 5-15 and in Biological Evaluation II, Figure 31 and pages 128-164 (particularly, see page 128, lines 11-13 and page 132, lines 14-18).

* * *

II. Rejection Under 35 USC §103(a)

The Office has rejected pending Claims 45-60 under 35 USC §103(a) as being unpatentable over WO 96/40257 (the "Alexander reference"), U.S. Patent No. 5,663,188 (the "Fossa reference"), and Dahlstrom et al. (Am. J. Cardiol., 1993; 71(3): 29A-33A) (the "Dahlstrom" reference). Applicants respectfully disagree and request withdrawal of this rejection. These references, either individually or collectively, do not teach or suggest using the claimed method to treat a subpopulation of subjects having heart failure post-acute myocardial infarction. In addition, these references provide no reasonable expectation that such subjects could be effectively treated using the claimed method.

Eplerenone (one of the three active ingredients specified in Claim 52) is the active ingredient in INSPRA™, a pharmaceutical product that was commercially launched in the United States in January 2004. The approved label for INSPRA™ specifically states at page 15:

> **INDICATIONS AND USAGE**
>
> **Congestive Heart Failure Post-Myocardial Infarction**
>
> INSPRA is indicated to improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction ≤ 40%) and clinical evidence of congestive heart failure after an acute myocardial infarction.

A copy of the approved label for INSPRA™ is attached as Exhibit A.

One of the clinical studies submitted to the Food and Drug Administration to support the registration of INSPRA™ for this indication was a morbidity and mortality study referred to as the EPHESUS study. In the EPHESUS study a subgroup of patients with heart failure post-acute myocardial infarction were administered eplerenone on top of standard of care therapy. Such standard of care therapy included treatment with angiotensin converting enzyme ("ACE") inhibitors and diuretics for a majority of the patients:

> At base line, the majority of patients were receiving standard therapies for acute myocardial infarction complicated by left ventricular dysfunction and heart failure, including ACE inhibitors or angiotensin-receptor blockers (in 87 percent of patients), beta-blockers (in 75 percent), aspirin (in 88 percent), and diuretics (in 60 percent).

New England Journal of Medicine, volume 348(14), 1309-21 (4 April 2003) at 1311. The results of the EPHESUS study are reported in greater detail in the New England Journal article. A copy of this article is attached as Exhibit B. In addition, the results the EPHESUS study also are summarized at pages 5 to 10 of the approved label for INSPRA™.

As reported in the New England Journal article, the general finding of the EPHESUS study was that "[t]he addition of eplerenone to optimal medical therapy reduces morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure." Id. at 1309. More specifically, the EPHESUS results indicated that the addition of eplerenone to optimal medical therapy for this subpopulation reduced (relative to patients receiving only the optimal medical therapy):

(1) death from cardiovascular causes;

(2) hospitalization for cardiovascular events;

(3) death from any cause;

(4) any hospitalization; and

(5) the rate of sudden death from cardiac causes.

Id. at 1313.

Further comments relating to the individual references cited by the Office are provided below:

(a) The Alexander Reference

The Alexander reference does not disclose or suggest treating a subpopulation of subjects having heart failure post-acute myocardial infarction by administering a combination of eplerenone, ramipril, and a loop diuretic, either generally or at the specific amounts recited in the claims. The primary focus of the Alexander reference is on a therapeutic combination comprising an epoxy-steroidal aldosterone antagonist, such as eplerenone (referred to as epoxymexrenone in the Alexander reference), an angiotensin II receptor antagonist (rather than an ACE inhibitor) and, optionally, a diuretic. An angiotensin II receptor antagonist is from an entirely distinct class of therapeutic agents than an ACE inhibitor.

With respect to the text cited by the Office at page 9, lines 21-24, of the Alexander reference regarding the combination of an ACE inhibitor and the aldosterone antagonist spironolactone, Applicants note that the complete discussion includes the passage:

> Clinical improvements have been reported for patients receiving a co-therapy of spironolactone and the ACE inhibitor enalapril, although this report mentions that controlled trials are needed to determine the lowest effective doses and to identify which patients would

benefit most from combined therapy . . . . (emphasis added).

MPEP 2141.02 clearly provides that the Office must consider the prior art in its entirety, including portions that would lead away from the claimed invention.

Given the focus of the Alexander reference on angiotensin II receptor antagonist combinations (rather than ACE inhibitor combinations) and the acknowledged need for additional clinical trials to identify the patients who would benefit from the discussed co-therapy of spironolactone and enalapril, this reference (1) fails to disclose or suggest treating a subpopulation of subjects having heart failure post-acute myocardial infarction by administering a combination of eplerenone, ramipril, and a loop diuretic, either generally or at the specific amounts recited in the claims, and (2) fails to provide a reasonable expectation that the claimed treatment would be successful.

(b) The Fossa Reference

The Fossa reference contains no disclosure relating to the use of an aldosterone antagonist generally, or to the use of eplerenone specifically. Instead, the focus of the Fossa reference is on combinations comprising either:

(i) an ACE inhibitor and an angiotensin II receptor antagonist, or

(ii) an ACE inhibitor and a renin inhibitor, or

(iii) a renin inhibitor and an angiotensin II receptor antagonist.

Like the Alexander reference discussed above, the Fossa reference (1) fails to disclose or suggest treating a subpopulation of subjects having heart failure post-acute

myocardial infarction by administering a combination of eplerenone, ramipril, and a loop diuretic, either generally or at the specific amounts recited in the claims, and (2) fails to provide a reasonable expectation that the claimed treatment would be successful.

(c) The Dahlstrom Reference

The Dahlstrom reference describes a study that reported "that rational therapy includes addition of the aldosterone antagonist spironolactone to low doses of captopril (or another ACE inhibitor) and high doses of loop diuretics, provided renal function is adequate" for patients having congestive heart failure. The Dahlstrom reference does not specifically mention eplerenone or disclose or suggest replacing spironolactone with eplerenone or any other aldosterone antagonist in such therapy. It also does not specifically mention ramipril. The Dahlstrom reference further focuses on the ACE inhibitor captopril administered at a low dose and notes that high doses of a loop diuretic should be co-administered with captopril for such therapy to be successful.

Like the Alexander reference and the Fossa reference discussed above, the Dahlstrom reference (1) fails to disclose or suggest treating a subpopulation of subjects having heart failure post-acute myocardial infarction by administering a combination of eplerenone, ramipril, and a loop diuretic, either generally or at the specific amounts recited in the claims, and (2) fails to provide a reasonable expectation that the claimed treatment would be successful.

Therefore the three references cited by the Office, either alone or in combination, do not teach or suggest the Applicants' invention as claimed in amended Claims 52-60. Accordingly, the aforementioned §103 objection should not be maintained against pending Claims 52-60, as amended.

*   *   *

Favorable consideration and early allowance of pending claims 52-60 is requested. Applicants respectfully request a two-month extension of time to and including August 27, 2006, for filing a response to the March 27, 2006 Office Action in this matter. The Commissioner is hereby authorized to charge the $450.00 fee for the requested two-month extension of time under 37 C.F.R. 1.16 and 1.17, together with any fees that may be required during the entire pendency of this application, to Deposit Account No. 19-1025.

Respectfully submitted,

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PHARMACIA CORPORATION
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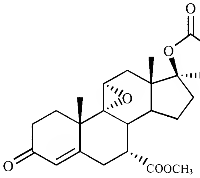
INSPRA™

eplerenone tablets

DESCRIPTION

INSPRA™ contains eplerenone, a blocker of aldosterone binding at the mineralocorticoid receptor.

Eplerenone is chemically described as Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ-lactone, methyl ester, (7α,11α,17α)-. Its empirical formula is $C_{24}H_{30}O_6$ and it has a molecular weight of 414.50. The structural formula of eplerenone is represented below:



eplerenone

Eplerenone is an odorless, white to off-white crystalline powder. It is very slightly soluble in water, with its solubility essentially pH independent. The octanol/water partition coefficient of eplerenone is approximately 7.1 at pH 7.0.

INSPRA for oral administration contains 25 mg or 50 mg of eplerenone and the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, hypromellose, sodium lauryl sulfate, talc, magnesium stearate, titanium dioxide, polyethylene glycol,

polysorbate 80, and iron oxide yellow and iron oxide red (25 mg tablet) and iron oxide red (50 mg tablct).

CLINICAL PHARMACOLOGY

Mechanism of Action

Eplcrenonc binds to the mineralocorticoid receptor and blocks the binding of aldosterone, a component of the renin-angiotensin-aldosterone-system (RAAS). Aldosterone synthesis, which occurs primarily in thc adrenal gland, is modulated by multiple factors, including angiotensin II and non-RAAS mediators such as adrenocorticotropic hormone (ACTH) and potassium. Aldosterone binds to mineralocorticoid receptors in both epithelial (e.g., kidney) and nonepithelial (e.g., heart, blood vessels, and brain) tissues and increases blood pressure through induction of sodium rcabsorption and possibly other mechanisms.

Eplerenonc has been shown to produce sustained increases in plasma renin and serum aldosteronc, consistent with inhibition of the negative regulatory feedback of aldosterone on renin secretion. Thc resulting incrcased plasma renin activity and aldosteronc circulating levels do not overcome the effects of eplcrenone.

Eplcrenonc selectively binds to rccombinant human mineralocorticoid receptors relative to its binding to recombinant human glucocorticoid, progesterone and androgen receptors.

Pharmacokinetics

General: Eplerenone is cleared predominantly by cytochrome P450 (CYP) 3A4 metabolism, with an climination half-life of 4 to 6 hours. Steady state is reached within 2 days. Absorption is not affected by food. Inhibitors of CYP3A4 (e.g., ketoconazole, saquinavir) increase blood lcvels of eplerenone.

Absorption and Distribution: Mean peak plasma concentrations of eplerenone are reached approximately 1.5 hours following oral administration. The absolute bioavailability of

eplerenone is unknown. Both peak plasma levels (C_{max}) and area under the curve (AUC) are dose proportional for doses of 25 to 100 mg and less than proportional at doses above 100 mg.

The plasma protein binding of eplerenone is about 50% and it is primarily bound to alpha 1-acid glycoproteins. The apparent volume of distribution at steady state ranged from 43 to 90 L. Eplerenone does not preferentially bind to red blood cells.

Metabolism and Excretion: Eplerenone metabolism is primarily mediated via CYP3A4. No active metabolites of eplerenone have been identified in human plasma.

Less than 5% of an eplerenone dose is recovered as unchanged drug in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 32% of the dose was excreted in the feces and approximately 67% was excreted in the urine. The elimination half-life of eplerenone is approximately 4 to 6 hours. The apparent plasma clearance is approximately 10 L/hr.

Special Populations

***Age, Gender, and Race*:** The pharmacokinetics of eplerenone at a dose of 100 mg once daily have been investigated in the elderly (≥65 years), in males and females, and in blacks. The pharmacokinetics of eplerenone did not differ significantly between males and females. At steady state, elderly subjects had increases in C_{max} (22%) and AUC (45%) compared with younger subjects (18 to 45 years). At steady state, C_{max} was 19% lower and AUC was 26% lower in blacks. (See **PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Geriatric Use and DOSAGE AND ADMINISTRATION, Hypertension**.)

***Renal Insufficiency*:** The pharmacokinetics of eplerenone were evaluated in patients with varying degrees of renal insufficiency and in patients undergoing hemodialysis. Compared with control subjects, steady-state AUC and C_{max} were increased by 38% and 24%, respectively, in patients with severe renal impairment and were decreased by 26% and 3%, respectively, in patients undergoing hemodialysis. No correlation was observed between plasma clearance of

eplerenone and creatinine clearance. Eplerenone is not removed by hemodialysis. (See **WARNINGS, Hyperkalemia in Patients Treated for Hypertension** and **PRECAUTIONS, Hyperkalemia in Patients Treated for Congestive Heart Failure Post-Myocardial Infarction and Congestive Heart Failure Post-Myocardial Infarction and Hypertension**.)

***Hepatic Insufficiency*:** The pharmacokinetics of eplerenone 400 mg have been investigated in patients with moderate (Child-Pugh Class B) hepatic impairment and compared with normal subjects. Steady-state C_{max} and AUC of eplerenone were increased by 3.6% and 42%, respectively. (See **DOSAGE AND ADMINISTRATION, Hypertension**.)

***Heart Failure*:** The pharmacokinetics of eplerenone 50 mg were evaluated in 8 patients with heart failure (NYHA classification II-IV) and 8 matched (gender, age, weight) healthy controls. Compared with the controls, steady state AUC and C_{max} in patients with stable heart failure were 38% and 30% higher, respectively.

Drug-Drug Interactions

(See **PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions**.)

Drug-drug interaction studies were conducted with a 100 mg dose of eplerenone.

Eplerenone is metabolized primarily by CYP3A4. A potent inhibitor of CYP3A4 (ketoconazole) caused increased exposure of about 5-fold while less potent CYP3A4 inhibitors (erythromycin, saquinavir, verapamil, and fluconazole) gave approximately 2-fold increases. Grapefruit juice caused only a small increase (about 25%) in exposure. (See **PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions** and **DOSAGE AND ADMINISTRATION, Hypertension**.)

Eplerenone is not an inhibitor of CYP1A2, CYP3A4, CYP2C19, CYP2C9, or CYP2D6. Eplerenone did not inhibit the metabolism of chlorzoxazone, diclofenac, methylphenidate, losartan, amiodarone, dexamethasone, mephobarbital, phenytoin, phenacetin, dextromethorphan,

metoprolol, tolbutamide, amlodipine, astemizole, cisapride, 17α-ethinyl estradiol, fluoxetine, lovastatin, methylprednisolone, midazolam, nifedipine, simvastatin, triazolam, verapamil, and warfarin in vitro. Eplerenone is not a substrate or an inhibitor of P-Glycoprotein at clinically relevant doses.

No clinically significant drug-drug pharmacokinetic interactions were observed when eplerenone was administered with digoxin, warfarin, midazolam, cisapride, cyclosporine, simvastatin, glyburide, or oral contraceptives (norethindrone/ethinyl estradiol). St. Johns Wort (a CYP3A4 inducer) caused a small (about 30%) decrease in eplerenone AUC.

No significant changes in eplerenone pharmacokinetics were observed when eplerenone was administered with aluminum and magnesium-containing antacids.

CLINICAL STUDIES

Congestive Heart Failure Post-Myocardial Infarction

The eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS) was a multinational, multicenter, double-blind, randomized, placebo-controlled study in patients clinically stable 3-14 days after an acute myocardial infarction (MI) with left ventricular dysfunction (as measured by left ventricular ejection fraction [LVEF] ≤40%) and either diabetes or clinical evidence of congestive heart failure (CHF) (pulmonary congestion by exam or chest x-ray or S_3). Patients with CHF of valvular or congenital etiology, patients with unstable post-infarct angina, and patients with serum potassium >5.0 mEq/L or serum creatinine >2.5 mg/dL were to be excluded. Patients were allowed to receive standard post-MI drug therapy and to undergo revascularization by angioplasty or coronary artery bypass graft surgery.

Patients randomized to INSPRA were given an initial dose of 25 mg once daily and titrated to the target dose of 50 mg once daily after 4 weeks if serum potassium was < 5.0 mEq/L. Dosage was reduced or suspended anytime during the study if serum potassium levels were ≥ 5.5 mEq/L. (See **DOSAGE AND ADMINISTRATION, Congestive Heart Failure Post-Myocardial Infarction**.)

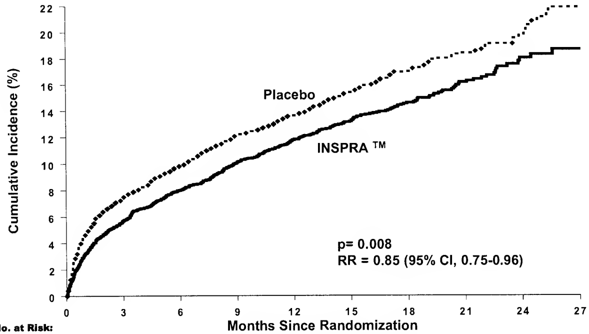
EPHESUS randomized 6,632 patients (9.3% U.S.) at 671 centers in 27 countries. The study population was primarily white (90%, with 1% black, 1% Asian, 6% Hispanic, 2% other) and male (71%). The mean age was 64 years (range, 22-94 years). The majority of patients had pulmonary congestion (75%) by exam or x-ray and were Killip Class II (64%). The mean ejection fraction was 33%. Thc average time to enrollment was 7 days post-MI. Medical histories prior to the index MI included hypertension (60%), coronary artery disease (62%), dyslipidemia (48%), angina (41%), type 2 diabetes (30%), previous MI (27%), and HF (15%).

The mean dose of INSPRA was 43 mg/day. Patients also received standard care including aspirin (92%), ACE inhibitors (90%), ß-blockers (83%), nitrates (72%), loop diuretics (66%), or HMG-CoA reductase inhibitors (60%).

Patients were followed for an average of 16 months (range, 0-33 months). The ascertainment rate for vital status was 99.7%.

The co-primary endpoints for EPHESUS were (1) the time to death from any cause, and (2) the time to first occurrcnce of cither cardiovascular (CV) mortality [defined as sudden cardiac death or dcath due to progrcssion of congestive heart failure (CHF), stroke, or other CV causes] or CV hospitalization (defined as hospitalization for progression of CHF, ventricular arrhythmias, acute myocardial infarction, or stroke). For the co-primary endpoint for death from any cause, there were 478 deaths in the INSPRA group (14.4%) and 554 deaths in the placebo group (16.7%). The risk of death with INSPRA was reduced by 15% [hazard ratio equal to 0.85 (95% confidence interval 0.75 to 0.96; p = 0.008 by log rank test)]. Kaplan-Meier estimates of all-cause mortality are shown in Figure 1 and the components of mortality are provided in Table 1.

Figure 1. Kaplan-Meier Estimates of All-Cause Mortality



No. at Risk:										
Placebo	3313	3064	2983	2830	2418	1801	1213	709	323	99
INSPRA ™	3319	3125	3044	2896	2463	1857	1260	728	336	110

Table 1. Components of All-Cause Mortality in EPHESUS

	INSPRA™ (N=3319) n (%)	Placebo (N=3313) n (%)	Hazard Ratio	p-value
Death from any cause	478 (14.4)	554 (16.7)	0.85	0.008
CV Death	407 (12.3)	483 (14.6)	0.83	0.005
Non-CV Death	60 (1.8)	54 (1.6)		
Unknown or unwitnessed death	11 (0.3)	17 (0.5)		

Most CV deaths were attributed to sudden death, acute MI, and CHF.

The time to first event for the co-primary endpoint of CV death or hospitalization as defined above, was longer in the INSPRA group (hazard ratio 0.87, 95% confidence interval 0.79 to 0.95, p = 0.002). An analysis that included the time to first occurrence of CV mortality and all CV hospitalizations (atrial arrhythmia, angina, CV procedures, progression of CHF, MI, stroke, ventricular arrhythmia, or other CV causes) showed a smaller effect with a hazard ratio of 0.92 (95% confidence interval 0.86 to 0.99; p = 0.028). The combined endpoints, including combined all-cause hospitalization and mortality were driven primarily by CV mortality. The combined endpoints in EPHESUS, including all-cause hospitalization and all-cause mortality, are presented in Table 2.

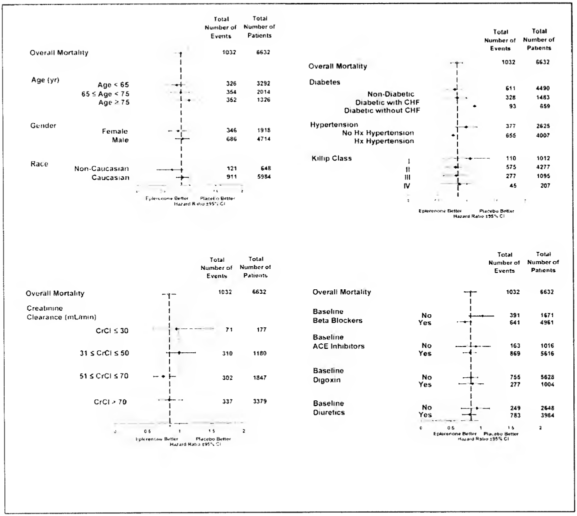
Table 2. Rates of Death or Hospitalization in EPHESUS

Event	INSPRA™ n (%)	Placebo n (%)
CV death or hospitalization for progression of CHF, stroke, MI or ventricular arrhythmia[1]	885 (26.7)	993 (30.0)
Death	407 (12.3)	483 (14.6)
Hospitalization	606 (18.3)	649 (19.6)
CV death or hospitalization for progression of CHF, stroke, MI, ventricular arrhythmia, atrial arrhythmia, angina, CV procedures, or other CV causes (PVD; Hypotension)	1516 (45.7)	1610 (48.6)
Death	407 (12.3)	483 (14.6)
Hospitalization	1281 (38.6)	1307 (39.5)
All-cause death or hospitalization	1734 (52.2)	1833 (55.3)
Death[1]	478 (14.4)	554 (16.7)
Hospitalization	1497 (45.1)	1530 (46.2)

[1] Co-Primary Endpoint.

Mortality hazard ratios varied for some subgroups as shown in Figure 2. Mortality hazard ratios appeared favorable for INSPRA for both genders and for all races or ethnic groups, although the numbers of non-caucasians were low (648, 10%). Patients with diabetes without clinical evidence of CHF and patients greater than 75 years did not appear to benefit from the use of INSPRA. Such subgroup analyses must be interpreted cautiously.

Figure 2. Hazard Ratios of All-Cause Mortality by Subgroups



Analyses conducted for a variety of CV biomarkers did not confirm a mechanism of action by which mortality was reduced.

Hypertension

The safety and efficacy of INSPRA have been cvaluated alone and in combination with other antihypertcnsive agents in clinical studies of 3091 hypertensive patients. The studies included 46% women, 14% blacks, and 22% elderly (age ≥65). The studies excluded patients with

elevated baseline serum potassium (>5.0 mEq/L) and elevated baseline serum creatinine (generally >1.5 mg/dL in males and >1.3 mg/dL in females).

Two fixed-dose, placebo-controlled, 8- to 12-week monotherapy studies in patients with baseline diastolic blood pressures of 95 to 114 mm Hg were conducted to assess the antihypertensive effect of INSPRA. In these two studies, 611 patients were randomized to INSPRA and 140 patients to placebo. Patients received INSPRA in doses of 25 to 400 mg daily as either a single daily dose or divided into two daily doses. The mean placebo-subtracted reductions in trough cuff blood pressure achieved by INSPRA in these studies at doses up to 200 mg are shown in Figures 3 and 4.

226

Figure 3. INSPRA™ Dose Response - Trough Cuff SBP Placebo-Subtracted Adjusted Mean Change from Baseline in Hypertension Studies

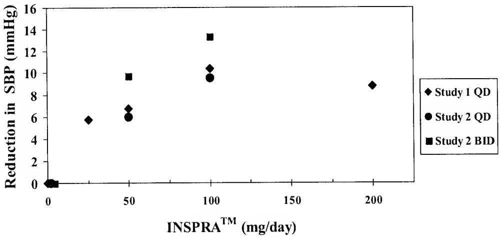
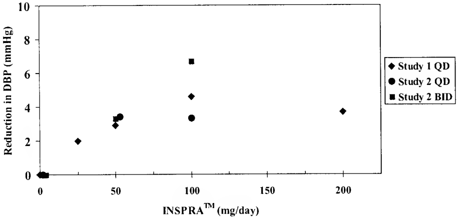


Figure 4. INSPRA™ Dose Response - Trough Cuff DBP Placebo-Subtracted Adjusted Mean Change from Baseline in Hypertension Studies



Patients treated with INSPRA 50 to 200 mg daily experienced significant decreases in sitting systolic and diastolic blood pressure at trough with differences from placebo of 6-13 mm Hg (systolic) and 3-7 mm Hg (diastolic). These effects were confirmed by assessments with 24-hour ambulatory blood pressure monitoring (ABPM). In these studies, assessments of 24-hour ABPM data demonstrated that INSPRA, administered once or twice daily, maintained antihypertensive efficacy over the entire dosing interval. However, at a total daily dose of 100 mg, INSPRA administered as 50 mg twice per day produced greater trough cuff (4/3 mm Hg) and ABPM (2/1 mm Hg) blood pressure reductions than 100 mg given once daily.

Blood pressure lowering was apparent within 2 weeks from the start of therapy with INSPRA, with maximal antihypertensive effects achieved within 4 weeks. Stopping INSPRA following treatment for 8 to 24 weeks in six studies did not lead to adverse event rates in the week following withdrawal of INSPRA greater than following placebo or active control withdrawal. Blood pressures in patients not taking other antihypertensives rose 1 week after withdrawal of INSPRA by about 6/3 mm Hg, suggesting that the antihypertensive effect of INSPRA was maintained through 8 to 24 weeks.

Blood pressure reductions with INSPRA in the two fixed-dose monotherapy studies and other studies using titrated doses, as well as concomitant treatments, were not significantly different when analyzed by age, gender, or race with one exception. In a study in patients with low renin hypertension, blood pressure reductions in blacks were smaller than those in whites during the initial titration period with INSPRA.

INSPRA has been studied concomitantly with treatment with ACE inhibitors, angiotensin II receptor antagonists, calcium channel blockers, beta blockers, and hydrochlorothiazide. When administered concomitantly with one of these drugs INSPRA usually produced its expected antihypertensive effects.

There was no significant change in average heart rate among patients treated with INSPRA in the combined clinical studies. No consistent effects of INSPRA on heart rate, QRS duration, or PR

or QT interval were observed in 147 normal subjects evaluated for electrocardiographic changes during pharmacokinetic studies.

INDICATIONS AND USAGE

Congestive Heart Failure Post-Myocardial Infarction

INSPRA is indicated to improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction ≤40%) and clinical evidence of congestive heart failure after an acute myocardial infarction. (See **CLINICAL STUDIES, Congestive Heart Failure Post-Myocardial Infarction**.)

Hypertension

INSPRA is indicated for the treatment of hypertension. INSPRA may be used alone or in combination with other antihypertensive agents. (See **CLINICAL STUDIES, Hypertension**.)

CONTRAINDICATIONS

INSPRA is contraindicated in all patients with the following:

- serum potassium >5.5 mEq/L at initiation
- creatinine clearance ≤30 mL/min
- concomitant use with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir. Inspra should also not be used with other drugs noted in the **CONTRAINDICATIONS, WARNINGS** or **PRECAUTIONS** sections of their labeling to be potent CYP3A4 inhibitors. (See **CLINICAL PHARMACOLOGY, Drug-Drug Interactions; PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions** and **DOSAGE AND ADMINISTRATION, Hypertension**.)

Hypertension

INSPRA is also contraindicated for the treatment of hypertension in patients with the following:

- type 2 diabetes with microalbuminuria

• serum creatinine >2.0 mg/dL in males or >1.8 mg/dL in females
• creatinine clearance <50 mL/min
• concomitant use of potassium supplements or potassium-sparing diuretics (amiloride, spironolactone, or triamterene)

(See **CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions; WARNINGS, Hyperkalemia in Patients Treated for Hypertension; PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions;** and **ADVERSE REACTIONS, Clinical Laboratory Test Findings, Hypertension, Potassium**.)

WARNINGS

Hyperkalemia in Patients Treated for Hypertension

The principal risk of INSPRA is hyperkalemia. Hyperkalemia can cause serious, sometimes fatal, arrhythmias. This risk can be minimized by patient selection, avoidance of certain concomitant treatments, and monitoring. For patient selection and avoidance of certain concomitant medications, see **CONTRAINDICATIONS; PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions;** and **ADVERSE REACTIONS, Clinical Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Potassium**. Periodic monitoring is recommended in patients at risk for the development of hyperkalemia (including patients receiving concomitant ACE inhibitors or angiotensin II receptor antagonists) until the effect of INSPRA is established. Dose reduction of INSPRA has been shown to decrease potassium levels. (See **DOSAGE AND ADMINISTRATION, Congestive Heart Failure Post-Myocardial Infarction and Hypertension**.)

PRECAUTIONS

Hyperkalemia in Patients Treated for Congestive Heart Failure Post-Myocardial Infarction

The principal risk of INSPRA is hyperkalemia. Hyperkalemia can cause serious, sometimes fatal, arrhythmias. Patients who develop hyperkalemia (>5.5 mEq/L) may still benefit from INSPRA with proper dose adjustment. Hyperkalemia can be minimized by patient selection, avoidance of certain concomitant treatments, and periodic monitoring until the effect of INSPRA has been established. For patient selection and avoidance of certain concomitant medications, see **CONTRAINDICATIONS; PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions;** and **ADVERSE REACTIONS, Clinical Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction, Potassium**. Dose reduction of INSPRA has been shown to decrease potassium levels. (See **DOSAGE AND ADMINISTRATION, Congestive Heart Failure Post-Myocardial Infarction**.)

Patients with CHF post MI who have serum creatinine levels >2.0 mg/dL (males) or >1.8 mg/dL (females) or creatinine clearance ≤50mL/min should be treated with caution. The rates of hyperkalemia increased with declining renal function. (See **ADVERSE REACTIONS, Clinical Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction, Potassium**.)

Diabetic patients with CHF post-MI, including those with proteinuria, should also be treated with caution. The subset of patients in EPHESUS with both diabetes and proteinuria on the baseline urinalysis had increased rates of hyperkalemia. (See **ADVERSE REACTIONS, Clinical Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction, Potassium**.)

Congestive Heart Failure Post-Myocardial Infarction and Hypertension

Impaired Hepatic Function: In 16 subjects with mild-to-moderate hepatic impairment who received 400 mg of eplerenone no elevations of serum potassium above 5.5 mEq/L were

observed. The mean increase in serum potassium was 0.12 mEq/L in patients with hepatic impairment and 0.13 mEq/L in normal controls. The use of INSPRA in patients with severe hepatic impairment has not been evaluated. (See **DOSAGE AND ADMINISTRATION** and **CLINICAL PHARMACOLOGY, Special Populations**.)

***Impaired Renal Function*:** (See **CONTRAINDICATIONS; WARNINGS;** and **PRECAUTIONS**.)

***Information for Patients*:** Patients receiving INSPRA should be informed not to use potassium supplements, salt substitutes containing potassium, or contraindicated drugs without consulting the prescribing physician. (See **CONTRAINDICATIONS; WARNINGS;** and **PRECAUTIONS**.)

***Drug Interactions*:**

Inhibitors of CYP3A4- Eplerenone metabolism is predominantly mediated via CYP3A4. A pharmacokinetic study evaluating the administration of a single dose of INSPRA 100 mg with ketoconazole 200 mg BID, a potent inhibitor of the CYP3A4 pathway, showed a 1.7-fold increase in C_{max} of eplerenone and a 5.4-fold increase in AUC of eplerenone. INSPRA should not be used with drugs described as strong inhibitors of CYP3A4 in their labeling. (See **CONTRAINDICATIONS**.)

Administration of eplerenone with other CYP3A4 inhibitors (e.g., erythromycin 500 mg BID, verapamil 240 mg QD, saquinavir 1200 mg TID, fluconazole 200 mg QD) resulted in increases in C_{max} of eplerenone ranging from 1.4- to 1.6-fold and AUC from 2.0- to 2.9-fold. (See **CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions** and **DOSAGE AND ADMINISTRATION, Hypertension**.)

ACE Inhibitors and Angiotensin II Receptor Antagonists (Congestive Heart Failure Post-Myocardial Infarction)- In EPHESUS, 3020 (91%) patients receiving INSPRA 25 to 50 mg also received ACE inhibitors or angiotensin II receptor antagonists (ACEI/ARB). Rates of patients with maximum potassium levels >5.5 mEq/L were similar regardless of the use of ACEI/ARB.

ACE Inhibitors and Angiotensin II Receptor Antagonists (Hypertension)- In clinical studies of patients with hypertension, the addition of INSPRA 50 to 100 mg to ACE inhibitors and angiotensin II receptor antagonists increased mean serum potassium slightly (about 0.09-0.13 mEq/L). In a study in diabetics with microalbuminuria INSPRA 200 mg combined with the ACE inhibitor enalapril 10 mg increased the frequency of hyperkalemia (serum potassium >5.5 mEq/L) from 17% on enalapril alone to 38%. (See **CONTRAINDICATIONS**.)

Lithium- A drug interaction study of eplerenone with lithium has not been conducted. Lithium toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors. Serum lithium levels should be monitored frequently if INSPRA is administered concomitantly with lithium.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)- A drug interaction study of eplerenone with an NSAID has not been conducted. The administration of other potassium-sparing antihypertensives with NSAIDs has been shown to reduce the antihypertensive effect in some patients and result in severe hyperkalemia in patients with impaired renal function. Therefore, when INSPRA and NSAIDs are used concomitantly, patients should be observed to determine whether the desired effect on blood pressure is obtained.

Pregnancy:

Pregnancy Category B- There are no adequate and well-controlled studies in pregnant women. INSPRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects- Embryo-fetal development studies were conducted with doses up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits (exposures up to 32 and 31 times the human AUC for the 100-mg/day therapeutic dose, respectively). No teratogenic effects were seen in rats or rabbits, although decreased body weight in maternal rabbits and increased rabbit fetal resorptions and post-implantation loss were observed at the highest administered dosage.

Because animal reproduction studies are not always predictive of human response, INSPRA should be used during pregnancy only if clearly needed.

Nursing Mothers: The concentration of eplerenone in human breast milk after oral administration is unknown. However preclinical data show that eplerenone and/or metabolites are present in rat breast milk (0.85:1 [milk:plasma] AUC ratio) obtained after a single oral dose. Peak concentrations in plasma and milk were obtained from 0.5 to 1 hour after dosing. Rat pups exposed by this route developed normally. Because many drugs are excreted in human milk and because of the unknown potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of INSPRA has not been established in pediatric patients.

Geriatric Use:

Congestive Heart Failure Post-Myocardial Infarction- Of the total number of patients in EPHESUS, 3340 (50%) were 65 and over, while 1326 (20%) were 75 and over. Patients greater than 75 years did not appear to benefit from the use of INSPRA. (See **CLINICAL STUDIES, Congestive Heart Failure Post-Myocardial Infarction**.) No differences in overall incidence of adverse events were observed between elderly and younger patients. However, due to age-related decreases in creatinine clearance, the incidence of laboratory-documented hyperkalemia was increased in patients 65 and older. (See **PRECAUTIONS, Hyperkalemia in Patients Treated for Congestive Heart Failure**.)

Hypertension- Of the total number of subjects in clinical hypertension studies of INSPRA, 1123 (23%) were 65 and over, while 212 (4%) were 75 and over. No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eplerenone was non-genotoxic in a battery of assays including in vitro bacterial mutagenesis (Ames test in *Salmonella* spp. and *E.*

Coli), in vitro mammalian cell mutagenesis (mouse lymphoma cells), in vitro chromosomal aberration (Chinese hamster ovary cells), in vivo rat bone marrow micronucleus formation, and in vivo/ex vivo unscheduled DNA synthesis in rat liver.

There was no drug-related tumor response in heterozygous P53 deficient mice when tested for 6 months at dosages up to 1000 mg/kg/day (systemic AUC exposures up to 9 times the exposure in humans receiving the 100-mg/day therapeutic dose). Statistically significant increases in benign thyroid tumors were observed after 2 years in both male and female rats when administered eplerenone 250 mg/kg/day (highest dose tested) and in male rats only at 75 mg/kg/day. These dosages provided systemic AUC exposures approximately 2 to 12 times higher than the average human therapeutic exposure at 100 mg/day. Repeat dose administration of eplerenone to rats increases the hepatic conjugation and clearance of thyroxin, which results in increased levels of TSH by a compensatory mechanism. Drugs that have produced thyroid tumors by this rodent-specific mechanism have not shown a similar effect in humans.

Male rats treated with eplerenone at 1000 mg/kg/day for 10 weeks (AUC 17 times that at the 100-mg/day human therapeutic dose) had decreased weights of seminal vesicles and epididymides and slightly decreased fertility. Dogs administered eplerenone at dosages of 15 mg/kg/day and higher (AUC 5 times that at the 100-mg/day human therapeutic dose) had dose-related prostate atrophy. The prostate atrophy was reversible after daily treatment for 1 year at 100 mg/kg/day. Dogs with prostate atrophy showed no decline in libido, sexual performance, or semen quality. Testicular weight and histology were not affected by eplerenone in any test animal species at any dosage.

ADVERSE REACTIONS

Congestive Heart Failure Post-Myocardial Infarction

In EPHESUS, safety was evaluated in 3307 patients treated with INSPRA and 3301 placebo-treated patients. The overall incidence of adverse events reported with INSPRA (78.9%) was similar to placebo (79.5%). Adverse events occurred at a similar rate regardless of age, gender,

or race. Patients discontinued treatment due to an adverse event at similar rates in either treatment group (4.4% INSPRA vs. 4.3% placebo).

Adverse events that occurred more frequently in patients treated with INSPRA than placebo were hyperkalemia (3.4% vs 2.0%) and increased creatinine (2.4% vs 1.5%). Discontinuations due to hyperkalemia or abnormal renal function were less than 1.0% in both groups. Hypokalemia occurred less frequently in patients treated with INSPRA (0.6% vs. 1.6%).

The rates of sex hormone related adverse events are shown in Table 3.

Table 3. Rates of Sex Hormone Related Adverse Events in EPHESUS

	Rates in Males			**Rates in Females**
	Gynecomastia	**Mastodynia**	**Either**	**Abnormal Vaginal Bleeding**
INSPRA™	0.4%	0.1%	0.5%	0.4%
Placebo	0.5%	0.1%	0.6%	0.4%

Hypertension

INSPRA has been evaluated for safety in 3091 patients treated for hypertension. A total of 690 patients were treated for over 6 months and 106 patients were treated for over 1 year.

In placebo-controlled studies, the overall rates of adverse events were 47% with INSPRA and 45% with placebo. Adverse events occurred at a similar rate regardless of age, gender, or race. Therapy was discontinued due to an adverse event in 3% of patients treated with INSPRA and 3% of patients given placebo. The most common reasons for discontinuation of INSPRA were headache, dizziness, angina pectoris/myocardial infarction, and increased GGT. The adverse events that were reported at a rate of at least 1% of patients and at a higher rate in patients treated with INSPRA in daily doses of 25 to 400 mg versus placebo are shown in Table 4.

Table 4. Rates (%) of Adverse Events Occurring in Placebo-Controlled Hypertension Studies in ≥1% of Patients Treated with INSPRA™ (25 to 400 mg) and at a More Frequent Rate than in Placebo-Treated Patients

	INSPRA™ (n=945)	Placebo (n=372)
Metabolic		
Hypercholesterolemia	1	0
Hypertriglyceridemia	1	0
Digestive		
Diarrhea	2	1
Abdominal pain	1	0
Urinary		
Albuminuria	1	0
Respiratory		
Coughing	2	1
Central/Peripheral Nervous System		
Dizziness	3	2
Body as a Whole		
Fatigue	2	1
Influenza-like symptoms	2	1

Note: Adverse events that are too general to be informative or are very common in the treated population are excluded.

Gynecomastia and abnormal vaginal bleeding were reported with INSPRA but not with placebo. The rates of these sex hormone related adverse events are shown in Table 5. The rates increased slightly with increasing duration of therapy. In females, abnormal vaginal bleeding was also reported in 0.8% of patients on antihypertensive medications (other than spironolactone) in active control arms of the studies with INSPRA.

Table 5. Rates of Sex Hormone Related Adverse Events with INSPRA™ in Hypertension Clinical Studies

	Rates in Males			Rates in Females
	Gynecomastia	Mastodynia	Either	Abnormal Vaginal Bleeding
All controlled studies	0.5%	0.8%	1.0%	0.6%
Controlled studies lasting ≥ 6 months	0.7%	1.3%	1.6%	0.8%
Open label, long-term study	1.0%	0.3%	1.0%	2.1%

Clinical Laboratory Test Findings

***Congestive Heart Failure Post-Myocardial Infarction*:**

Creatinine- Increases of more than 0.5 mg/dL were reported for 6.5% of patients administered INSPRA and for 4.9% of placebo-treated patients.

Potassium- In EPHESUS, the frequency of patients with changes in potassium (<3.5 mEq/L or >5.5 mEq/L or ≥6.0 mEq/L) receiving INSPRA compared with placebo are displayed in Table 6.

Table 6. Hypokalemia (<3.5 mEq/L) or Hyperkalemia (>5.5 or ≥6.0 mEq/L) in EPHESUS

Potassium (mEq/L)	INSPRA™ (N=3251) n (%)	Placebo (N=3237) n (%)
< 3.5	273 (8.4)	424 (13.1)
>5.5	508 (15.6)	363 (11.2)
≥ 6.0	180 (5.5)	126 (3.9)

Table 7 shows the rates of hyperkalemia in EPHESUS as assessed by baseline renal function (creatinine clearance).

Table 7. Rates of Hyperkalemia (>5.5 mEq/L) in EPHESUS by Baseline Creatinine Clearance*

Baseline Creatinine Clearance	INSPRA™	Placebo
≤30 mL/min	31.5%	22.6%
31-50 mL/min	24.1%	12.7%
51-70 mL/min	16.9%	13.1%
>70 mL/min	10.8%	8.7%

* Estimated using the Cockroft-Gault formula.

Table 8 shows the rates of hyperkalemia in EPHESUS as assessed by two baseline characteristics: presence/absence of proteinuria from baseline urinalysis and presence/absence of diabetes. (See **PRECAUTIONS, Hyperkalemia in Patients Treated for Congestive Heart Failure**.)

Table 8. Rates of Hyperkalemia (>5.5 mEq/L) in EPHESUS by Proteinuria and History of Diabetes*

	INSPRA™	Placebo
Proteinuria, no Diabetes	16%	11%
Diabetes, no Proteinuria	18%	13%
Proteinuria and Diabetes	26%	16%

*Diabetes assessed as positive medical history at baseline; proteinuria assessed by positive dipstick urinalysis at baseline.

Hypertension:

Potassium- In placebo-controlled fixed-dose studies, the mean increases in serum potassium were dose related and are shown in Table 9 along with the frequencies of values >5.5 mEq/L.

Table 9. Changes in Serum Potassium in the Placebo-Controlled, Fixed-Dose Hypertension Studies of INSPRA™

		Mean Change mEq/L	**% >5.5 mEq/L**
Daily Dosage	**n**		
Placebo	194	0	1
25	97	0.08	0
50	245	0.14	0
100	193	0.09	1
200	139	0.19	1
400	104	0.36	8.7

Patients with both type 2 diabetes and microalbuminuria are at increased risk of developing persistent hyperkalemia. In a study in such patients taking INSPRA 200 mg, the frequencies of maximum serum potassium levels >5.5 mEq/L were 33% with INSPRA given alone and 38% when INSPRA was given with enalapril.

Rates of hyperkalemia increased with decreasing renal function. In all studies serum potassium elevations >5.5 mEq/L were observed in 10.4% of patients treated with INSPRA with baseline calculated creatinine clearance <70 mL/min, 5.6% of patients with baseline creatinine clearance of 70 to 100 mL/min, and 2.6% of patients with baseline creatinine clearance of >100 mL/min. (See **WARNINGS, Hyperkalemia in Patients Treated for Hypertension**.)

Sodium- Serum sodium decreased in a dose-related manner. Mean decreases ranged from 0.7 mEq/L at 50 mg daily to 1.7 mEq/L at 400 mg daily. Decreases in sodium (<135 mEq/L) were reported for 2.3% of patients administered INSPRA and 0.6% of placebo-treated patients.

Triglycerides- Serum triglycerides increased in a dose-related manner. Mean increases ranged from 7.1 mg/dL at 50 mg daily to 26.6 mg/dL at 400 mg daily. Increases in triglycerides (above 252 mg/dL) were reported for 15% of patients administered INSPRA and 12% of placebo-treated patients.

Cholesterol- Serum cholesterol increased in a dose-related manner. Mean changes ranged from a decrease of 0.4 mg/dL at 50 mg daily to an increase of 11.6 mg/dL at 400 mg daily. Increases in serum cholesterol values greater than 200 mg/dL were reported for 0.3% of patients administered INSPRA and 0% of placebo-treated patients.

Liver Function Tests- Serum alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT) increased in a dose-related manner. Mean increases ranged from 0.8 U/L at 50 mg daily to 4.8 U/L at 400 mg daily for ALT and 3.1 U/L at 50 mg daily to 11.3 U/L at 400 mg daily for GGT. Increases in ALT levels greater than 120 U/L (3 times upper limit of normal) were reported for 15/2259 patients administered INSPRA and 1/351 placebo-treated patients. Increases in ALT levels greater than 200 U/L (5 times upper limit of normal) were reported for 5/2259 of patients administered INSPRA and 1/351 placebo-treated patients. Increases of ALT greater than 120 U/L and bilirubin greater than 1.2 mg/dL were reported 1/2259 patients administered INSPRA and 0/351 placebo-treated patients. Hepatic failure was not reported in patients receiving INSPRA.

BUN/Creatinine- Serum creatinine increased in a dose-related manner. Mean increases ranged from 0.01 mg/dL at 50 mg daily to 0.03 mg/dL at 400 mg daily. Increases in blood urea nitrogen to greater than 30 mg/dL and serum creatinine to greater than 2 mg/dL were reported for 0.5% and 0.2%, respectively, of patients administered INSPRA and 0% of placebo-treated patients.

Uric Acid- Increases in uric acid to greater than 9 mg/dL were reported in 0.3% of patients administered INSPRA and 0% of placebo-treated patients.

OVERDOSAGE

No cases of human overdosage with eplerenone have been reported. Lethality was not observed in mice, rats, or dogs after single oral doses that provided C_{max} exposures at least 25 times higher than in humans receiving eplerenone 100 mg/day. Dogs showed emesis, salivation, and tremors at a C_{max} 41 times the human therapeutic C_{max}, progressing to sedation and convulsions at higher exposures.

The most likely manifestation of human overdosage would be anticipated to be hypotension or hyperkalemia. Eplerenone cannot be removed by hemodialysis. Eplerenone has been shown to bind extensively to charcoal. If symptomatic hypotension should occur, supportive treatment should be instituted. If hyperkalemia develops, standard treatment should be initiated.

DOSAGE AND ADMINISTRATION

Congestive Heart Failure Post-Myocardial Infarction

The recommended dose of INSPRA is 50 mg once daily. Treatment should be initiated at 25 mg once daily and titrated to the target dose of 50 mg once daily preferably within 4 weeks as tolerated by the patient. INSPRA may be administered with or without food.

Serum potassium should be measured before initiating INSPRA therapy, within the first week and at one month after the start of treatment or dose adjustment. Serum potassium should be assessed periodically thereafter. Factors such as patient characteristics and serum potassium levels may indicate that additional monitoring is appropriate. (See **PRECAUTIONS, Hyperkalemia in Patients Treated for Congestive Heart Failure** and **ADVERSE REACTIONS, Clinical Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction, Potassium**.) In EPHESUS, the majority of hyperkalemia was observed within the first three months after randomization. The dose should be adjusted based on the serum potassium level and the dose adjustment table shown below (Table 10).

Table 10. Dose Adjustment in Congestive Heart Failure

Serum Potassium (mEq/L)	Action	Dose Adjustment
< 5.0	Increase	25mg QOD to 25mg QD 25mg QD to 50mg QD
5.0-5.4	Maintain	No adjustment
5.5-5.9	Decrease	50mg QD to 25mg QD 25mg QD to 25mg QOD 25mg QOD to withhold
≥ 6.0	Withhold	

Following withholding INSPRA due to serum potassium ≥6.0 mEq/L, INSPRA can be restarted at a dose of 25 mg QOD when serum potassium levels have fallen below 5.5 mEq/L.

Hypertension

INSPRA may be used alone or in combination with other antihypertensive agents. The recommended starting dose of INSPRA is 50 mg administered once daily. The full therapeutic effect of INSPRA is apparent within 4 weeks. For patients with an inadequate blood pressure response to 50 mg once daily the dosage of INSPRA should be increased to 50 mg twice daily. Higher dosages of INSPRA are not recommended either because they have no greater effect on blood pressure than 100 mg or because they are associated with an increased risk of hyperkalemia. (See **CLINICAL STUDIES, Hypertension**.)

No adjustment of the starting dose is recommended for the elderly or for patients with mild-to-moderate hepatic impairment. For patients receiving weak CYP3A4 inhibitors, such as erythromycin, saquinavir, verapamil, and fluconazole the starting dose should be reduced to 25 mg once daily. (See **CONTRAINDICATIONS** and **PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions**.)

HOW SUPPLIED

INSPRA Tablets, 25 mg, are yellow diamond biconvex film-coated tablets. They are debossed with *PHA* on one side and 1710 on the other. They are supplied as follows:

NDC Number	Size
0025-1710-01	Bottle of 30 tablets
0025-1710-02	Bottle of 90 tablets
0025-1710-03	Hospital Unit Dose

INSPRA Tablets, 50 mg, are pink diamond biconvex film-coated tablets. They are debossed with *PHA* on one side and 1720 on the other. They are supplied as follows:

NDC Number	Size
0025-1720-03	Bottle of 30 tablets
0025-1720-01	Bottle of 90 tablets

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

Rx only Revised: Date

U.S. Patent No. 4,559,332

INSPRA Tablets are manufactured for:

G.D. Searle LLC

A subsidiary of Pharmacia Corporation

Chicago, IL 60680, USA.

Date Copy Code

October 7, 2003

EXHIBIT B

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Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction

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ABSTRACT

BACKGROUND

Aldosterone blockade reduces mortality and morbidity among patients with severe heart failure. We conducted a double-blind, placebo-controlled study evaluating the effect of eplerenone, a selective aldosterone blocker, on morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.

METHODS

Patients were randomly assigned to eplerenone (25 mg per day initially, titrated to a maximum of 50 mg per day; 3313 patients) or placebo (3319 patients) in addition to optimal medical therapy. The study continued until 1012 deaths occurred. The primary end points were death from any cause and death from cardiovascular causes or hospitalization for heart failure, acute myocardial infarction, stroke, or ventricular arrhythmia.

RESULTS

During a mean follow-up of 16 months, there were 478 deaths in the eplerenone group and 554 deaths in the placebo group (relative risk, 0.85; 95 percent confidence interval, 0.75 to 0.96; P=0.008). Of these deaths, 407 in the eplerenone group and 483 in the placebo group were attributed to cardiovascular causes (relative risk, 0.83; 95 percent confidence interval, 0.72 to 0.94; P=0.005). The rate of the other primary end point, death from cardiovascular causes or hospitalization for cardiovascular events, was reduced by eplerenone (relative risk, 0.87; 95 percent confidence interval, 0.79 to 0.95; P=0.002), as was the secondary end point of death from any cause or any hospitalization (relative risk, 0.92; 95 percent confidence interval, 0.86 to 0.98; P=0.02). There was also a reduction in the rate of sudden death from cardiac causes (relative risk, 0.79; 95 percent confidence interval, 0.64 to 0.97; P=0.03). The rate of serious hyperkalemia was 5.5 percent in the eplerenone group and 3.9 percent in the placebo group (P=0.002), whereas the rate of hypokalemia was 8.4 percent in the eplerenone group and 13.1 percent in the placebo group (P<0.001).

CONCLUSIONS

The addition of eplerenone to optimal medical therapy reduces morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.

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ALDOSTERONE BLOCKADE REDUCES THE rate of death due to progressive heart failure and the rate of sudden death from cardiac causes, as well as the rate of hospitalizations for heart failure, among patients with severe heart failure due to systolic left ventricular dysfunction who are being treated with an angiotensin-converting–enzyme (ACE) inhibitor.[1] Aldosterone blockade also prevents ventricular remodeling and collagen formation in patients with left ventricular dysfunction after acute myocardial infarction[2] and affects a number of pathophysiological mechanisms that are thought to be important in the prognosis of patients with acute myocardial infarction.[3-12] Its role in reducing mortality and the rate of hospitalization among patients with acute myocardial infarction complicated by left ventricular dysfunction is uncertain. We therefore designed the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) to test the hypothesis that treatment with eplerenone, an aldosterone blocker that selectively blocks the mineralocorticoid receptor and not glucocorticoid, progesterone, or androgen receptors,[13] reduces overall mortality and cardiovascular mortality or hospitalization for cardiovascular events among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure who are receiving optimal medical therapy.

METHODS

STUDY DESIGN AND STUDY POPULATION

We conducted a multicenter, international, randomized, double-blind, placebo-controlled trial.[14] Patients were randomly assigned to receive eplerenone (25 mg per day) or matching placebo for four weeks, after which the dose of eplerenone was increased to a maximum of 50 mg per day. Randomization was stratified according to clinical site, and schedules were prepared with the use of permuted blocks to ensure the ongoing equivalence of the size of the groups. If at any time during the study the serum potassium concentration was higher than 5.5 mmol per liter, the dose of the study drug was reduced or treatment was temporarily discontinued until the serum potassium concentration fell below 5.5 mmol per liter.

Patients in whom the following criteria were met were eligible for randomization 3 to 14 days after acute myocardial infarction: acute myocardial infarction as documented according to standard criteria; left ventricular dysfunction as documented by a left ventricular ejection fraction of 40 percent or lower on echocardiography, radionuclide angiography, or angiography of the left ventricle after the index acute myocardial infarction and before randomization; and heart failure as documented by the presence of pulmonary rales, chest radiography showing pulmonary venous congestion, or the presence of a third heart sound. In patients with diabetes who met the criteria for left ventricular dysfunction after acute myocardial infarction, symptoms of heart failure did not have to be demonstrated, since such patients have an increased risk of cardiovascular events similar to that of nondiabetic patients with symptoms of heart failure.[15] Patients received optimal medical therapy, which could include ACE inhibitors, angiotensin-receptor blockers, diuretics, and beta-blockers, as well as coronary reperfusion therapy.

Important criteria for exclusion were the use of potassium-sparing diuretics, a serum creatinine concentration of more than 2.5 mg per deciliter (220 μmol per liter), and a serum potassium concentration of more than 5.0 mmol per liter before randomization. The institutional review board or ethics committee at each site approved the protocol, and all patients provided written informed consent before enrollment.

Screening and base-line procedures were to be performed during the hospitalization for the index acute myocardial infarction, and follow-up visits occurred at one and four weeks, three months, and every three months thereafter until the termination of the study. The serum potassium concentration was measured 48 hours after the initiation of treatment, at one, four, and five weeks, at all scheduled study visits, and within one week after any change of dose. Information about adverse events and concurrent medications was recorded at every visit. All patients who underwent randomization were followed for vital status and hospitalizations every three months until the termination of the study.

DEFINITION OF STUDY END POINTS

The two primary end points were time to death from any cause and time to death from cardiovascular causes or first hospitalization for a cardiovascular event, including heart failure, recurrent acute myocardial infarction, stroke, or ventricular arrhythmia. The major secondary end points were death from cardiovascular causes and death from any cause or any hospitalization. All end points were adjudicat-

ed by a blinded critical-events committee. Definitions of all adjudicated end points are presented in Supplementary Appendix 1 (available with the full text of this article at http://www. nejm.org).

STATISTICAL ANALYSIS

The two groups were compared in terms of the two primary end points and the secondary end points with the use of Cox proportional-hazards regression. The Cox model included a single covariate corresponding to treatment group and was stratified according to geographic region (Canada and the United States, Latin America, eastern Europe, western Europe, and the rest of the world [including Australia, Israel, New Zealand, South Africa, South Korea, and Taiwan]). The model was used to estimate the relative risk and corresponding 95 percent confidence interval. Time-to-event distributions were summarized with Kaplan–Meier curves. For analyses of mortality, data were censored at the time of loss to follow-up or on the closing date of the study (August 30, 2002). For analyses of death from cardiovascular causes or hospitalization for cardiovascular events, data were censored at the time of death due to noncardiovascular causes, the time of loss to follow-up, or on the closing date of the study. Analyses of the primary and secondary end points were conducted according to the intention-to-treat principle.

The trial was designed to enroll 6200 patients and to continue until 1012 deaths occurred. To maintain an overall type I error rate of 0.05 (two-sided), the rate of death from any cause was tested at the 0.04 level of significance and the rate of death from cardiovascular causes or hospitalization for cardiovascular events was tested at the 0.01 level of significance. With testing at the 0.04 level of significance (two-sided), the study had 88.3 percent power to detect an 18.5 percent difference between the two groups in the rate of death from any cause.[16] An external data and safety monitoring board conducted four interim analyses; an alpha level of 0.0001 was the threshold for early termination in the first two interim analyses of mortality from any cause, and an alpha level of 0.001 was the threshold for the last two analyses. Data-base management was performed by a contract research organization. The interim analyses were conducted by an independent statistician for the data and safety monitoring board. All final analyses were conducted by the sponsor. All independent authors had a substantial role in trial design, data accrual, and data interpretation. All had complete access to the data after unblinding.

Subgroup analyses for the two primary end points were performed with a Cox model stratified according to region, with terms for treatment, subgroup, and interaction between treatment and subgroup. For these analyses, measured variables were treated as binary variables, dichotomized at the median value, and also considered as continuous variables.

We also used Cox regression to summarize the time to first hospitalization for a cardiovascular event. For these analyses, data were censored at the time of death. The frequencies of hospitalization for particular causes were analyzed by means of a Cochran–Mantel–Haenszel test, and the relative risk for this analysis was reported as the ratio of the number of hospitalizations per patient in the eplerenone group to the number of hospitalizations per patient in the placebo group. The number of patients who would need to be treated to prevent one event was determined by the method of Altman and Andersen.[17]

All patients who received at least one dose of the study medication were included in the safety analyses, which included analyses of adverse events, vital signs, and results of clinical laboratory tests. Changes in vital signs and clinical laboratory values were assessed by analysis of covariance, with the base-line value as a covariate. Creatinine clearance was calculated according to the Cockcroft–Gault formula.[18] All reported P values are two-sided and are not adjusted for the interim analyses.

RESULTS

STUDY PATIENTS

A total of 6642 patients underwent randomization at 674 centers in 37 countries between December 27, 1999, and December 31, 2001. A total of 3313 were assigned to placebo, 3319 were assigned to eplerenone, and 10 were excluded from the analysis before unblinding because of problems with the quality of the data at one center. There were no significant differences between the two groups at base line (Table 1). At base line, the majority of patients were receiving standard therapies for acute myocardial infarction complicated by left ventricular dysfunction and heart failure, including ACE inhibitors or angiotensin-receptor blockers (in 87 percent of patients), beta-blockers (in 75 percent), aspirin (in 88 percent), and diuretics (in 60 percent).

Twelve patients in each treatment group did not take any study medication. During the study, 1021 patients (493 in the placebo group and 528 in the eplerenone group) permanently discontinued the

study medication (median time from randomization to the last dose, 98 days). The most frequent reasons were a request by the patient to withdraw from the study (in 204 patients in the placebo group and 231 in the eplerenone group) and adverse events (in 149 patients in the placebo group and 147 in the eplerenone group). Seventeen patients (7 in the placebo group and 10 in the eplerenone group) had unknown vital status on the closing date of the study (August 30, 2002), and 99 percent of the surviving patients were seen or contacted between August 15 and August 30, 2002. The mean duration of follow-up was 16 months (range, 0 to 33). The mean dose-equivalent of study medication was 43.5 mg in the placebo group and 42.6 mg in the eplerenone group.

Table 1. **Base-Line Characteristics of the Patients.***

Characteristic	Eplerenone Group (N=3319)	Placebo Group (N=3313)
Age — yr	64±11	64±12
Race — no. (%)†		
White	2995 (90)	2989 (90)
Black	30 (1)	44 (1)
Other	294 (9)	280 (8)
Sex — no. (%)		
Male	2380 (72)	2334 (70)
Female	939 (28)	979 (30)
Blood pressure — mm Hg		
Systolic	119±17	119±17
Diastolic	72±11	72±11
Left ventricular ejection fraction — %	33±6	33±6
Days from myocardial infarction to randomization	7.3±3.0	7.3±3.0
Previous hospitalization for heart failure — %	7	8
Reperfusion therapy or revascularization — %	45	45
Symptoms of heart failure — %	90	90
Serum potassium concentration — mmol/liter	4.3±0.4	4.3±0.5
Serum creatinine concentration — mg/dl‡	1.1±0.3	1.1±0.3
Creatinine clearance — ml/min	79±60	78±57
Medical history — %		
Acute myocardial infarction	27	27
Diabetes	32	32
Heart failure	14	15
Hypertension	60	61
Medications — %§		
ACE inhibitor or angiotensin-receptor blocker	86	87
Beta-blockers	75	75
Diuretics	60	61
Aspirin	88	89
Statins	47	47

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme.

† Race was self-reported by patients.

‡ To convert values for creatinine to micromoles per liter, multiply by 88.4.

§ Data are for medications taken at randomization or up to 14 days after the index acute myocardial infarction.

END POINTS

A total of 478 patients in the eplerenone group (14.4 percent) and 554 patients in the placebo group (16.7 percent) died (relative risk, 0.85; P=0.008) (Table 2). Kaplan–Meier estimates of mortality at one year were 11.8 percent in the eplerenone group and 13.6 percent in the placebo group (Fig. 1A). The end point of death from cardiovascular causes or hospitalization for cardiovascular events was reached by 885 patients in the eplerenone group (26.7 percent) and 993 patients in the placebo group (30.0 percent) (relative risk, 0.87; P=0.002) (Fig. 1B).

A total of 407 deaths in the eplerenone group (12.3 percent of patients) and 483 deaths in the placebo group (14.6 percent of patients) were attributed to cardiovascular causes (relative risk, 0.83; P=0.005). The reduction in cardiovascular mortality was similar for the most common causes — sudden death from cardiac causes, acute myocardial infarction, and heart failure (range of relative risks, 0.79 to 0.82). Of these reductions, the reduction in the risk of sudden death from cardiac causes was statistically significant (relative risk, 0.79; P=0.03) (Table 2 and Fig. 1C). There was a relative reduction of 15 percent in the risk of hospitalization for heart failure with eplerenone (relative risk, 0.85; P=0.03), and there were 23 percent fewer episodes of hospitalization for heart failure in the eplerenone group than in the placebo group (relative risk, 0.77; P=0.002). The rate of death from any cause or any hospitalization was 8 percent lower in the eplerenone group than in the placebo group (relative risk, 0.92; P=0.02).

The relative risks for important predefined subgroups are shown in Figure 2. Reductions in the rate of death from any cause and the rate of death from cardiovascular causes or hospitalization for cardiovascular events were consistent among subgroups. Interactions between treatment and some measured variables were significant when they

Table 2. **Summary of Primary and Secondary End Points.***

Variable	Eplerenone Group (N=3319)	Placebo Group (N=3313)	Relative Risk (95% CI) or Ratio†	P Value
Primary end points				
Death from any cause (no. of patients)	478	554	0.85 (0.75–0.96)	0.008
Death from cardiovascular causes or hospitalization for cardiovascular events (no. of patients)	885	993	0.87 (0.79–0.95)	0.002
Secondary end points				
Death from any cause or any hospitalization (no. of patients)	1730	1829	0.92 (0.86–0.98)	0.02
Death from cardiovascular causes (no. of patients)	407	483	0.83 (0.72–0.94)	0.005
Sudden death from cardiac causes	162	201	0.79 (0.64–0.97)	0.03
Acute myocardial infarction	78	94	0.82 (0.61–1.10)	0.19
Heart failure	104	127	0.80 (0.62–1.04)	0.10
Stroke	26	28	0.91 (0.53–1.55)	0.73
Other	37	33	1.00 (0.60–1.66)	0.99
Any hospitalization (no. of patients)	1493	1526	0.95 (0.89–1.02)	0.20
Hospitalization for cardiovascular events (no. of patients)	606	649	0.91 (0.81–1.01)	0.09
Acute myocardial infarction	224	229	0.97 (0.80–1.16)	0.71
Heart failure	345	391	0.85 (0.74–0.99)	0.03
Stroke	70	51	1.34 (0.94–1.93)	0.11
Ventricular arrhythmia	52	54	0.95 (0.65–1.39)	0.79
Any hospitalization (no. of episodes)	2815	2984	0.94	0.12
Hospitalization for cardiovascular events (no. of episodes)	876	1004	0.87	0.03
Acute myocardial infarction	268	269	0.99	0.96
Heart failure	477	618	0.77	0.002
Stroke	73	54	1.35	0.11
Ventricular arrhythmia	58	63	0.92	0.69

* Hospitalizations were defined as nonfatal events causing or prolonging hospitalization. CI denotes confidence interval.
† Numbers without confidence intervals are the ratios of the number of hospitalizations per patient in the eplerenone group to the number of hospitalizations per patient in the placebo group.

were analyzed as binary variables with median cutoff points (e.g., pulse pressure), but when they were considered as continuous variables, the interactions were no longer significant. The beneficial effect of eplerenone was also consistent across geographic regions (P=0.24 for the interaction of treatment and region for death from any cause, and P=0.94 for the interaction of treatment and region for death from cardiovascular causes or hospitalization for cardiovascular events).

SAFETY

After week 1, the mean systolic and diastolic blood pressure increased in both groups from base line to each time point throughout the remainder of the trial. The magnitude of these increases in the

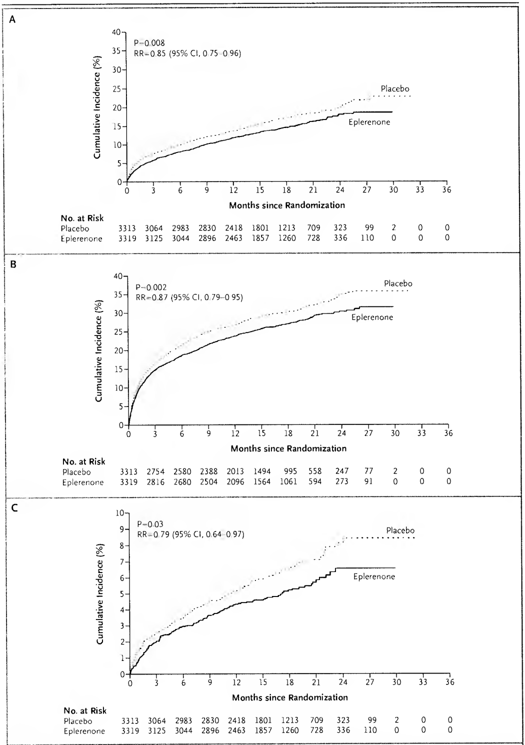


Figure 1. **Kaplan–Meier Estimates of the Rate of Death from Any Cause (Panel A), the Rate of Death from Cardiovascular Causes or Hospitalization for Cardiovascular Events (Panel B), and the Rate of Sudden Death from Cardiac Causes (Panel C).** RR denotes relative risk, and CI confidence interval.

eplerenone group was significantly smaller than that in the placebo group at every point. At one year, the mean blood pressure had increased by 8/4 mm Hg in the placebo group and by 5/3 mm Hg in the eplerenone group ($P<0.01$). Also at one year, the heart rate had decreased by 6 beats per minute in the placebo group and by 7 beats per minute in the eplerenone group ($P=0.32$).

At one year, the serum creatinine concentration had increased by 0.02 mg per deciliter (1.8 μmol per liter) in the placebo group and by 0.06 mg per deciliter (5.3 μmol per liter) in the eplerenone group ($P<0.001$). Potassium levels had increased in both groups at one year (by 0.2 mmol per liter in the placebo group and 0.3 mmol per liter in the eplerenone group, $P<0.001$). Serious hyperkalemia (serum potassium concentration, ≥6.0 mmol per liter) occurred in 5.5 percent of patients in the eplerenone group, as compared with 3.9 percent of those in the placebo group ($P=0.002$). For patients who had serious hyperkalemia, the incidence of greater elevations in the potassium concentration was similar in the eplerenone group (0.6 percent with concentrations ≥7 mmol per liter and 0.2 percent with concentrations ≥8 mmol per liter) and in the placebo group (0.5 percent with concentrations ≥7 mmol per liter and 0.1 percent with concentrations ≥8 mmol per liter). Fifteen patients with serious hyperkalemia (12 in the eplerenone group and 3 in the placebo group) were hospitalized for the condition, and one death in the placebo group was attributed to it. In each treatment group, the incidence of hyperkalemia was higher among patients with a lower base-line creatinine clearance ($P<0.001$ by logistic-regression analysis). Among patients with a base-line creatinine clearance of less than 50 ml per minute, the incidence of serious hyperkalemia was 10.1 percent in the eplerenone group and 5.9 percent in the placebo group ($P=0.006$). Among patients with a base-line creatinine clearance of 50 ml per minute or more, the corresponding rates were 4.6 percent and 3.5 percent ($P=0.04$). Patients who had serious hyperkalemia were also more likely than those who did not have serious hyperkalemia to have a serum potassium concentration of more than 5.5 mmol per liter or a calculated creatinine clearance of less than 70 ml per minute at the week 1 visit.

There were no other significant differences between the treatment groups in the number of patients with changes in laboratory variables that met prespecified criteria for abnormally low or high values. Adverse events are described in Table 3.

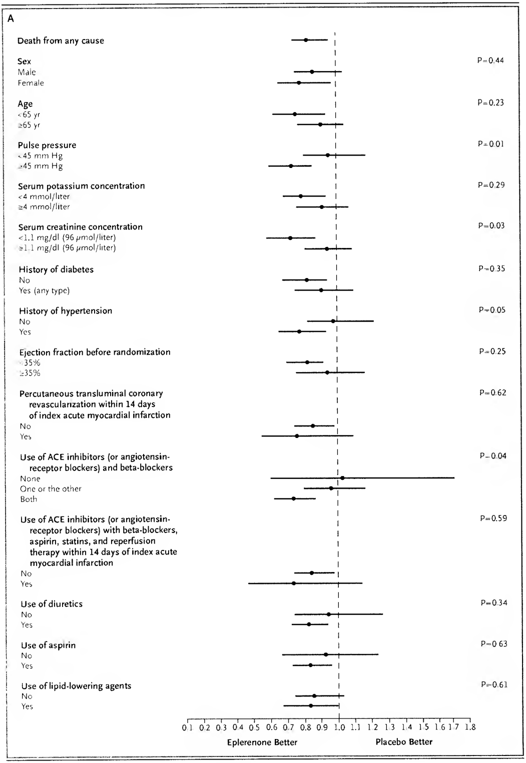
DISCUSSION

The addition of eplerenone to optimal treatment at a maximal dose of 50 mg once daily (mean dose, 43 mg per day) in patients assigned to treatment 3 to 14 days (mean, 7) after acute myocardial infarction resulted in additional reductions in overall mortality and the rate of death from cardiovascular causes or hospitalization for cardiovascular events among patients whose acute myocardial infarction was complicated by left ventricular dysfunction and heart failure. There was also a reduction in cardiovascular mortality and the rate of death from any cause or any hospitalization among patients assigned to eplerenone.

One-year mortality among patients assigned to placebo, the majority of whom received an ACE inhibitor or angiotensin-receptor blocker and a beta-blocker, was 13.6 percent. This rate is higher than that in the treatment groups of a recent study of carvedilol in patients with left ventricular dysfunction after acute myocardial infarction (the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction [CAPRICORN] study) and a study of losartan in patients with left ventricular dysfunction after acute myocardial infarction (the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan [OPTIMAAL]),[19,20] in which control patients were treated with an ACE inhibitor and a beta-blocker; the higher rate in our study most likely reflects the presence of signs of heart failure, in addition to left ventricular dysfunction, in 90 percent of our patients. Mortality in the placebo group in the current study, however, was lower and the

Figure 2. **Relative Risks of Death from Any Cause (Panel A, next page) and Relative Risks of Death from Cardiovascular Causes or Hospitalization for Cardiovascular Events (Panel B, page 1317), According to Base-Line Demographic and Clinical Characteristics.**

Horizontal lines represent 95 percent confidence intervals. Values for age, pulse pressure, serum potassium concentration, serum creatinine concentration, and ejection fraction were dichotomized at the median. Analyses according to the use or nonuse of an angiotensin-converting–enzyme (ACE) inhibitor (or angiotensin-receptor blocker), a beta-blocker, or both; according to the use of an ACE inhibitor (or angiotensin-receptor blocker) with a beta-blocker, aspirin, statins, and reperfusion therapy up to 14 days after the index acute myocardial infarction; according to the use of diuretics; and according to the use of lipid-lowering agents were post hoc analyses.


A
Death from any cause
Sex
Male
Female
P=0.44
Age
<65 yr
≥65 yr
P=0.23
Pulse pressure
<45 mm Hg
≥45 mm Hg
P=0.01
Serum potassium concentration
<4 mmol/liter
≥4 mmol/liter
P=0.29
Serum creatinine concentration
<1.1 mg/dl (96 μmol/liter)
≥1.1 mg/dl (96 μmol/liter)
P=0.03
History of diabetes
No
Yes (any type)
P=0.35
History of hypertension
No
Yes
P=0.05
Ejection fraction before randomization
<35%
≥35%
P=0.25
Percutaneous transluminal coronary revascularization within 14 days of index acute myocardial infarction
No
Yes
P=0.62
Use of ACE inhibitors (or angiotensin-receptor blockers) and beta-blockers
None
One or the other
Both
P=0.04
Use of ACE inhibitors (or angiotensin-receptor blockers) with beta-blockers, aspirin, statins, and reperfusion therapy within 14 days of index acute myocardial infarction
No
Yes
P=0.59
Use of diuretics
No
Yes
P=0.34
Use of aspirin
No
Yes
P=0.63
Use of lipid-lowering agents
No
Yes
P=0.61
0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8
Eplerenone Better
Placebo Better

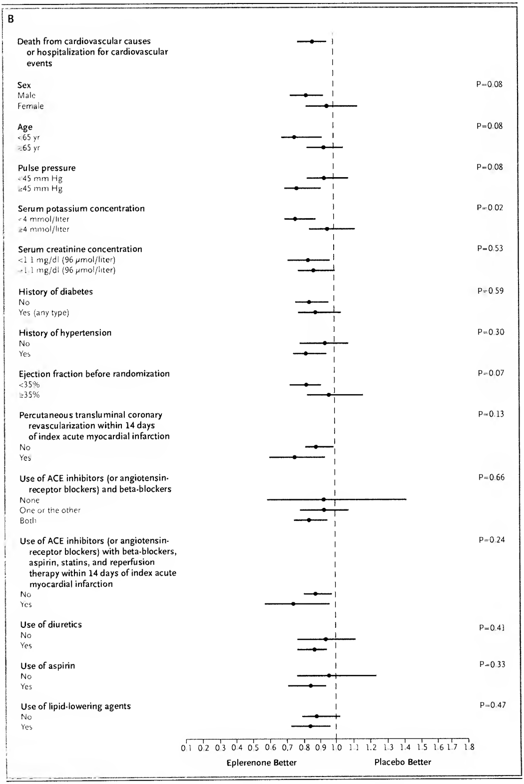

B
Death from cardiovascular causes or hospitalization for cardiovascular events
Sex
Male
Female
P=0.08
Age
<65 yr
≥65 yr
P=0.08
Pulse pressure
<45 mm Hg
≥45 mm Hg
P=0.08
Serum potassium concentration
<4 mmol/liter
≥4 mmol/liter
P=0.02
Serum creatinine concentration
<1.1 mg/dl (96 μmol/liter)
≥1.1 mg/dl (96 μmol/liter)
P=0.53
History of diabetes
No
Yes (any type)
P=0.59
History of hypertension
No
Yes
P=0.30
Ejection fraction before randomization
<35%
≥35%
P=0.07
Percutaneous transluminal coronary revascularization within 14 days of index acute myocardial infarction
No
Yes
P=0.13
Use of ACE inhibitors (or angiotensin-receptor blockers) and beta-blockers
None
One or the other
Both
P=0.66
Use of ACE inhibitors (or angiotensin-receptor blockers) with beta-blockers, aspirin, statins, and reperfusion therapy within 14 days of index acute myocardial infarction
No
Yes
P=0.24
Use of diuretics
No
Yes
P=0.41
Use of aspirin
No
Yes
P=0.33
Use of lipid-lowering agents
No
Yes
P=0.47
0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8
Eplerenone Better
Placebo Better

Table 3. **Adverse Events.**

Adverse Event	Eplerenone Group (N=3307)	Placebo Group (N=3301)	P Value
	no. of patients (%)		
≥1 Event	2608 (78.9)	2623 (79.5)	0.57
Cardiovascular disorder*	1606 (48.6)	1661 (50.3)	0.16
Respiratory disorder	729 (22.0)	803 (24.3)	0.03
Cough	167 (5.0)	207 (6.3)	0.03
Dyspnea	243 (7.3)	307 (9.3)	0.004
Pneumonia	92 (2.8)	123 (3.7)	0.03
Metabolic or nutritional disorder	568 (17.2)	635 (19.2)	0.03
Hyperkalemia†	113 (3.4)	66 (2.0)	<0.001
Hypoglycemia	20 (0.6)	35 (1.1)	0.04
Hypokalemia†	15 (0.5)	49 (1.5)	<0.001
Hyperuricemia	87 (2.6)	111 (3.4)	0.08
Neoplasm	57 (1.7)	58 (1.8)	0.93
Urinary tract disorder	473 (14.3)	419 (12.7)	0.06
Disorder of skin or appendages	220 (6.7)	223 (6.8)	0.88
Musculoskeletal disorder	209 (6.3)	213 (6.5)	0.84
Nervous system disorder	492 (14.9)	449 (13.6)	0.14
Psychiatric disorder	238 (7.2)	272 (8.2)	0.12
Gastrointestinal disorder	659 (19.9)	583 (17.7)	0.02
Endocrine disorder	34 (1.0)	23 (0.7)	0.18
Disorder in men‡	59 (2.5)	65 (2.8)	0.53
Gynecomastia	12 (0.5)	14 (0.6)	0.70
Impotence	21 (0.9)	20 (0.9)	1.00
Disorder in women§	17 (1.8)	17 (1.7)	1.00
Breast pain	1 (0.1)	3 (0.3)	0.63
Serious hyperkalemia (serum potassium ≥6 mmol/liter)¶	180 (5.5)	126 (3.9)	0.002
Serious hypokalemia (serum potassium <3.5 mmol/liter)¶	273 (8.4)	424 (13.1)	<0.001

* Data are for all cardiovascular adverse events reported, whether or not they were related to a study end point.
† Data are based on investigators' reports.
‡ There were 2326 men in the placebo group and 2370 men in the eplerenone group.
§ There were 975 women in the placebo group and 937 women in the eplerenone group.
¶ Data are based on laboratory measurements. Data were available for 3237 patients in the placebo group and 3251 in the eplerenone group.

magnitude of the effect of aldosterone blockade was smaller than in the Randomized Aldactone Evaluation Study (RALES), a trial of spironolactone in patients with left ventricular dysfunction and severe chronic heart failure.[1] These differences may be attributable to several factors, including the greater use of beta-blockers and a higher base-line left ventricular ejection fraction in the current study. In RALES,[1] the mean left ventricular ejection fraction at base line was 25 percent, and patients had New York Heart Association class III or IV heart failure, whereas in the current study in patients with acute myocardial infarction, the mean left ventricular ejection fraction was 33 percent at base line and may have improved after reperfusion, recovery of ventricular stunning, or both. The severity of left ventricular dysfunction,[21] the degree of heart failure, and the intensity of background therapy are most likely important factors determining the absolute mortality as well as the effectiveness of therapeutic agents.

The reduction in cardiovascular mortality was in large part due to a 21 percent reduction in the rate of sudden death from cardiac causes. Reductions in the rate of death due to progressive heart failure and acute myocardial infarction were similar but not significant. The reduction in the rate of hospitalization for cardiovascular events was largely due to a 15 percent reduction in the risk of hospitalization for heart failure and a 23 percent reduction in the number of episodes of hospitalization for heart failure. The mechanisms by which eplerenone provides myocardial protection in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure are not completely clear. Effects of aldosterone blockers on plasma volume and electrolyte excretion have been recognized for many years, and although these effects may have contributed to the benefit provided by eplerenone, other nonrenal mechanisms may be equally or more important. Eplerenone reduces coronary vascular inflammation and the risk of subsequent development of interstitial fibrosis in animal models of myocardial disease.[22,23] Eplerenone also reduces oxidative stress, improves endothelial dysfunction,[4,24] attenuates platelet aggregation,[4] decreases activation of matrix metalloproteinases, and improves ventricular remodeling.[25] In addition, aldosterone blockade decreases sympathetic drive in rats through direct actions in the brain,[26] improves norepinephrine uptake in patients with heart failure,[3] and improves heart-rate variability[27]

— all factors known to have important effects on the risk of sudden death from cardiac causes.

Eplerenone was beneficial in patients who were receiving optimal therapy including an ACE inhibitor or angiotensin-receptor blocker, a beta-blocker, aspirin, a lipid-lowering agent, and coronary reperfusion therapy. Previous experience with regard to the effectiveness of aldosterone blockade in patients with left ventricular dysfunction who are receiving an ACE inhibitor and a beta-blocker is limited, in that in RALES the proportion of patients who were treated with a beta-blocker was only 11 percent.[1] This difference in treatments is important, because ACE inhibitors and beta-blockers are considered to represent the current standard of care in patients with left ventricular dysfunction after acute myocardial infarction, and other treatments, including endothelin-receptor antagonists, antibodies against tumor necrosis factor α, and angiotensin-receptor blockers, have not been found to reduce mortality among patients with left ventricular dysfunction and heart failure who are being treated with an ACE inhibitor and a beta-blocker.

We examined a number of predefined subgroups, but our trial was not designed with sufficient power to draw statistical conclusions about individual subgroups. Thus, one should be cautious in interpreting the results of subgroup analyses. There were a few subgroups in which we found a nominally significant interaction with treatment, but no interaction we examined had a significant effect on both primary end points. In general, the beneficial effect of eplerenone on the two primary end points was consistent.

There was an increased incidence of serious hyperkalemia among patients assigned to eplerenone. The risk of serious hyperkalemia was significantly increased among patients who had a decreased creatinine clearance at base line (<50 ml per minute). Although there were no deaths in the eplerenone group that were attributed to hyperkalemia, this finding emphasizes the need to monitor serum potassium and adjust the dose of eplerenone accordingly. We attempted to minimize the risk of hyperkalemia by excluding patients with a base-line serum potassium concentration of more than 5.0 mmol per liter, a base-line serum creatinine concentration of more than 2.5 mg per deciliter, or both. It should, however, be emphasized that in elderly patients, patients with a low body-mass index, or patients with diabetes mellitus, the serum creatinine concentration may not accurately reflect renal function. Determination of creatinine clearance by the Cockcroft–Gault formula, exclusion of patients with moderate-to-severe renal insufficiency, use of a loop diuretic in those with mild renal insufficiency, and adherence to the range of doses used in this study (25 to 50 mg per day) should minimize the risk of hyperkalemia among patients receiving eplerenone and further improve the risk–benefit ratio of this drug. It should also be pointed out that the risk of hypokalemia was more than twice as high as the risk of serious hyperkalemia and that eplerenone significantly reduced this risk.

The rate of discontinuation of blinded treatment due to adverse events and the rates of adverse events other than hyperkalemia and a variety of minor gastrointestinal complications in patients receiving eplerenone were low. In particular, the incidence of gynecomastia and impotence among men in the eplerenone group was no greater than that in the placebo group. This finding differs from the findings in RALES[1] and can be attributed to the fact that eplerenone has greater selectivity for the mineralocorticoid receptor than does spironolactone, which also binds to androgen and progesterone receptors. The benefit of eplerenone in reducing the risk of respiratory disorders most likely reflects its reduction of the rate of recurrent heart failure, whereas its benefit in reducing the risk of metabolic and nutritional disorders largely reflects a reduced incidence of hypokalemia and hypoglycemia.

In conclusion, with an estimated number needed to treat of 50 to save one life in one year and an estimated number needed to treat of 33 to prevent one death from cardiovascular causes or one hospitalization for a cardiovascular event in one year, the addition of eplerenone to optimal medical therapy contributes to the continued improvement in survival and hospitalization rates among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.

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Drs. Pitt and Zannad report having served as consultants to Pharmacia.

APPENDIX

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